REMARKS

I. Status of Claims and Claim Amendments

In this amendment, claims 64-65 have been added. New claims 64-65 specify that the M1 protein contains the amino acid sequence Tyr-Lys-Lys-Leu (YKKL) at residues 100-103. Support for new claims 64-65 can be found, for example, in Example 1, Example 12, and Example 13, and SEQ ID NO:3 (see protein translation filed as Exhibit A). No new matter has been introduced.

After entry of this amendment, claims 34 to 65 will be pending. The Office Action dated March 12, 2008 has been carefully reviewed and the following reply is made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 34-42 and 45-63 under 35 U.S.C. § 103(a) as obvious under Latham *et al.* (*J. of Virology* 75, 6154-6165) in view of Saito *et al.* (*Vaccine* 2001, Vol. 20, 125-133).

Specifically, the Examiner asserts that he has made a *prima facie* case of obviousness because:

> The VLPs of Latham *et al.* react with monoclonal antibodies in western blots and on fixed cells and are stated by Latham *et al.* to be useful as vaccines. The VLPs are shown to look like influenza particles (Figure 5). The proteins that make the VLP of Latham *et al.* appear to be wild type in structure and antibody binding. The VLPs of Latham *et al.* would be expected to have the HA and NA activity of influenza. The claims recite no structures that differentiate them from the VLPs of Latham *et al.* (2/16/06 Action).

Page 3, July 13, 2007 Office Action.

Moreover, the Examiner asserts that inherency can be used in a rejection under 35 U.S.C. § 103(a) and points to MPEP 2112 V, stating:

> Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference. The PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product.

Page 4, March 12, 2008 Office Action (quoting *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980)).

As noted above, the Examiner asserts that the burden has shifted to the Applicants to show an unobvious difference and prove that the prior art products do not possess the characteristics of the claimed product.

To this end, Applicants show below that the VLPs of the present invention contain structural differences as compared to the VLPs disclosed by Latham *et al.*, and that these differences result in the unexpected property of increased VLP formation from Sf9 and other suitable cells. In support of Applicants' position, filed herewith is the Declaration of Dr. Gale Smith, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Smith Declaration").

Unexpected Results

Applicants have shown previously that the production of VLPs comprising the M1 protein derived from avian influenza virus strains is far superior to the production of VLPs comprising M1 derived from human influenza strains. See, *e.g.*, paragraphs 4 and 4a of the Smith Declaration.[1]

Applicants now show that a structural feature found in the avian M1 (a "YKKL" L-domain at amino acid positions 100-103) is vital to the formation of VLPs and results in the unexpected property of increased VLP formation. See, generally, the Smith Declaration.

Applicants have found that avian influenza virus strains, including A/Hong Kong/1073/99 of the present application, contain the sequence "YKKL" at amino acids 100-103 of the M1 protein. In contrast, human influenza strains, including the human seasonal strain A/Udorn/72 as disclosed by Latham *et al.*, were found to contain a defective "YRKL" L-domain. See *Id.* at paragraphs 5 and 5a, and corresponding amino acid alignments in Exhibits 2 and 3.

The Smith Declaration describes experiments comparing VLP production between YRKL L-domain containing strains and YKKL mutants generated by site-directed mutagenesis (*i.e.* an R101K mutation). *Id.* at paragraph 6. Applicants show that the YKKL containing

[1] Applicants would like to bring to the Examiner's attention an error in paragraph 5 of the Declaration filed December 17, 2007. The fraction comprising the VLPs was collected "from the middle of the gradient at about 40% sucrose," and not "from the top of the gradient." The technical error has been corrected in the Declaration filed herewith.

mutants produce significantly more VLPs than their YRKL containing counterparts. *Id.* at paragraphs 6a and 7.

Furthermore, the Smith declaration shows a dramatic difference in VLP formation between YKKL containing avian strains such as A/Hong Kong/1073/99 (H9N2) (disclosed in the present application) compared to the YRKL containing human seasonal strain of Latham *et al.* (A/Udorn/72). *Id.* at paragraph 8.

Moreover, the Applicants show that the YKKL L-domain is found almost exclusively in M1 derived from avian influenza strains. Among the 40 M1 proteins found to harbor the "YKKL" L-domain, 39 are found from avian strains. *Id.* at paragraph 9.

Thus, Applicants show that the claimed invention possesses a structural feature (the YKKL L-domain of avian M1) that results in an unexpected property that increases the level of VLP from Sf9 or other suitable cells. Moreover, Applicants have shown that the avian M1 is a superior protein for the formation of VLPs than the seasonal M1 disclosed by Latham *et al.* Such superiority of a property shared with the prior art is evidence of non-obviousness (Although Applicants note that the phrase "a property shared" is used loosely given the poor ability of the Latham *et al.* M1 to produce VLPs). Applicants direct the Examiner's attention to MPEP 716.02(a) II, which states:

> Evidence of unobvious or **unexpected advantageous properties, such as superiority in a property** the claimed compound shares with the prior art, **can rebut *prima facie* obviousness**. (emphasis added).

MPEP 716.02(a) II also states:

> Evidence that a compound is **unexpectedly superior in one of a spectrum of common properties**...can be enough to rebut a prima facie case of obviousness. No set number of examples of superiority is required. *In re Chapp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987).

Applicants respectfully submit that the ability to assemble is an M1 driven property of a VLP. Thus, the enhanced ability of avian M1 containing VLPs to assemble represents a unexpectedly superior property of the claimed VLPs. Accordingly, Applicants have shown an unexpected property of the product as requested by the Examiner (see Office Action, page 5).

Furthermore, Applicants have demonstrated that this superior property is of "both statistical and practical significance." See MPEP 716.02(b), citing *Ex Parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Evidence of unexpected properties may be in the form of a direct…comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See MPEP 716.02(b) III, citing *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). Applicants have shown that use of the seasonal human M1 of Latham *et al.* produces only a mere fraction of the VLPs as compared to when avian M1 proteins are used, such as those disclosed in the present application (see Smith Declaration at paragraph 8b, which shows that the YRKL L-domain containing Udorn M1 of Latham *et al.* yields only 12% of the level of that produced by the YKKL L-domain containing avian M1). Applicants respectfully submit that this difference is clearly statistically significant.

Furthermore, Applicants respectfully submit that such a statistically significant unexpected result is also of enormous practical significance. The increased formation and recovery of VLPs with avian M1 is critical to vaccine development. Using a human seasonal M1 protein such as the Udorn M1 disclosed by Latham *et al.* does not produce sufficient quantities of VLPs for use in a vaccine. See *Id.* at 12. The only viable way to make recoverable amounts of VLPs necessary for vaccine production is through the use of avian derived M1 proteins, such as those disclosed in the present application. *Id.*

Applicants respectfully submit that the prior art provides no teaching or suggestion to use avian M1 to produce VLPs. Moreover, one of ordinary skill in the art would not have been motivated to use avian M1 based on the teachings of Latham *et al.* One of ordinary skill in the art knows that the surface influenza glycoproteins HA and NA are the primary targets for elicitation of protective immunity against influenza targets. Therefore, one of ordinary skill in the art would have had no motivation to use avian M1, which confers no relevant immunogenicity. Based on the teachings of Latham *et al.*, one of ordinary skill in the art would arguably have been motivated to use the seasonal human M1 of A/Udorn/72 to produce VLPs, and Applicants have shown that the use of seasonal human M1 proteins leads to insufficient VLP production. The deficiencies of Latham *et al.* are not cured by Saito *et al.*, which provides no teaching or suggestion for the use of avian M1 for VLP production.

Accordingly, Applicants have shown that the invention as claimed possesses a structural feature (the "YKKL" L-domain of M1) resulting in an unexpected property and that such an unexpected property is evidence of unobviousness. Moreover, because the prior art provides no teaching, suggestion, or motivation for using the avian M1 for producing VLPs, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

Improper Obviousness Rejections

a. Applicants kindly acknowledge the Examiner's presentation of *In re Napier*, 34 USPQ2d 1782 regarding inherency in the context of obviousness (See Office Action, page 3). However, Applicants respectfully submit that the Examiner's analysis of *In re Napier* as it applies to the instant claims is incorrect.

Pending claim 34 specifies that the VLP exhibits hemagglutinin or neuraminidase activity. Applicants assert that none of the cited references disclose an influenza VLP, wherein the HA and/or the NA exhibit activity, let alone an avian VLP wherein the HA and/or NA exhibit activity. Although Examiner asserts that the expression of HA and NA are well known in the art to have enzymatic activity (Office Action mailed March 27, 2007), the Examiner has failed to provide a satisfactory reference to support such an assertion, particularly in a VLP (see below). Applicants respectfully submit that the Examiner does not know if the VLPs of Latham *et al.* exhibit HA or NA activity, and that this lack of knowledge is important in the context of the obviousness determination.

While inherency can apply to some obviousness determinations (e.g. *In re Napier*), Applicant stresses that the concepts of obviousness and inherent anticipation are not the same. See *Trintec Indus., Inc. v. TOP-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002) ("obviousness is not inherent anticipation"). As stated in *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), "a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." Additionally, "obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known.") (emphasis added). Because the suggestion to combine or modify references must occur prior to an applicant's date of invention, an unknown inherency cannot supply this suggestion at the required time. *In re Rijckaert* at 1534 (emphasis

added). Accordingly, the reference cited by the Examiner (Matassov *et al.*, *Viral Immunology*, September 1, 2007, 20(3): 441-452) to show HA and NA activity cannot be used to show the VLPs of Latham *et al.* inherently possessed HA and NA activity because it was published after the filing date of the present application.

Furthermore, Applicants point out that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic" (emphasis added). If the HA and NA activity limitation is inherently disclosed in the art, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *Continental Can*, 948 F.2d at 1268-1269 (Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.) In insisting that there is inherent disclosure of the HA and NA activity in the art, the Examiner bears an evidentiary burden to establish that the limitation was necessarily present. In this case, the Examiner provides no evidence of such activity prior to the filing date of the instant application. Applicants invite the Examiner to submit documentary evidence that HA and/or NA in Latham *et al.* have activity or the Examiner must take Official Notice without documentary evidence to support the his conclusion (see MPEP 2144.03). Otherwise, Applicants assert that the rejections under 35 U.S.C. § 103 should be withdrawn due to lack of evidence.

b. The Examiner has rejected claims 34, and 43-44 under 35 U.S.C. § 103(a) as being unpatentable over Latham *et al.* and Saito *et al.* and Gupta *et al.* (Vaccine 2001, Vol 14: 219-225). Specifically, the Examiner asserts that Latham *et al.* discloses VLPs, Saito *et al.* discloses avian influenza, and Gupta *et al.* discloses Novasomes, thus rendering the claims obvious.

Applicants traverse this rejection and assert that the Examiner has not met his burden of establishing a *prima facie* case of obviousness. "To establish a *prima facie* case of obviousness of a claimed invention, all claim limitation must be taught or suggested by the prior art" (MPEP 2143.03). As stated above, Latham *et al.* does not show nor suggest that the HA or NA exhibit activity, as required by the claims (see above arguments). This deficiency is not cured by the teachings of Saito *et al.* In addition, Gupta *et al.* does not disclose influenza vaccines in combination with adjuvants. Thus, the combined references do not teach or suggest all the claim elements. Therefore, the Examiner has not established a *prima facie* case of obviousness. In

view of the above argument, Applicants request that this rejection be reconsidered and withdrawn.

Summary

In summary, Applicants assert that the Declaration of Dr. Gale Smith, Ph.D., filed under 37 C.F.R. § 1.132 presents evidence of unexpected results, and thereby evidence of unobviousness. In addition, Applicants assert that the Examiner has mistakenly used an inherency analysis to support an obviousness rejection in the context of the present claims and has thus not met his burden of establishing a *prima facie* case of obviousness.

Conclusion

The foregoing amendments and remarks are being made to place this application in condition for allowance. Applicants await favorable action. If the Examiner believes that an interview would be helpful to resolve any remaining issues in this application, the Examiner is invited to telephone the undersigned at the number below.

Please charge the fee for a three-month extension of time to our Deposit Account No. 50-1283. Please charge any additional fees deemed necessary and please credit any overpayments to the Deposit Account.

Dated: September 12, 2008

Respectfully submitted,
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